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L6: Entry 3 of 5 File: USPT Mar 6, 2001

DOCUMENT-IDENTIFIER: US 6197349 B1
TITLE: Particles with modified physicochemical properties, their preparation and uses

ABPL:
which have a mean particle size of between 30 and 500 nm, and disperse compositions containing them, as administration forms and delivery systems for drugs, vaccines and other biologically active agents such as herbicides, pesticides, insecticides, fungicides, fertilizers, vitamins, nutrition additives and cosmetics.

BSPR:
The present invention is in the area of administration forms and delivery systems for drugs, vaccines and other biologically active agents such as herbicides. pesticides, insecticides, fungicides, fertilizers. vitamins, nutrition additives and cosmetics. More specifically, the invention is related to particles comprising an interior phase of ubidecarenone or of other poorly water-soluble substances characterized in that these substances, which are solid and primarily crystalline at room temperature in the bulk phase, are primarily present in an amorphous, preferably liquid, physical state in the particles, e.g. as a supercooled melt, hereinafter being referred to as particles of supercooled melts (PSM); to fine dispersions of PSMs in a dispersion medium of pharmaceutically acceptable liquids, preferably aqueous media; as well as to the method of manufacture and the use of such particles and dispersions as delivery systems for the parenteral, enteral, peroral, oral, nasal, pulmonal, ophthalmic, mucosal or (trans)dermal administration of poorly water-soluble bioactive agents, particularly drugs; and to their use in cosmetic, food and agricultural products.

BSPR:
Numerous poorly water-soluble bioactive substances, e.g. drugs, are present as solid, in particular crystalline bulk materials at room temperature, primarily in the form of poorly wettable powders with grain sizes in the micro- and millimeter size range. In many cases drugs which share these properties exhibit a poor bioavailability, particularly upon peroral administration. Bioavailability is defined as the rate and the extent of absorption of a bioactive agent into the blood compartment and of the distribution to its site of action. The low absorption rate of poorly water-soluble, in particular lipophilic substances from the gastrointestinal tract (GIT) is generally attributed to the poor solubility of these substances and to their poor wettability in gastrointestinal fluids. Industrially manufactured bioactive substances have generally particle sizes well above 1 .mu.m since they are preferably processed from cruder materials by mechanical comminution such as milling and micronization. In some cases precipitation from organic solvents is applied. Sjostrom et al. (Sjostrom B., Kronberg B., Carlfors J., J. Pharm. Sci. 82 (1993) 579-583) describe the manufacturing of submicron drug particles by precipitation in solvent containing o/w emulsions. The method is based on the use of potentially harmful organic solvents such as toluene and chlorinated hydrocarbons. From the technical point, it is virtually impossible to completely remove the solvents from the product so that the solid drug particles contain solvent residues which present a toxicological risk. Moreover, the use of volatile and inflammable organic solvents requires special precautions with respect to manufacturing safety.

BSPR:
In case of extravasal administration of solid drugs with the objective of a systemic drug action, the dissolution process of the substance can become the rate limiting step in absorption and might thus lead to a poor bioavailability.

It is common knowledge that the dissolution rate of a substance is affected inter alia by its particle size, its wettability and with crystalline substances also by the energy required to overcome lattice forces. It can therefore be deduced that the bioavailability of poorly water-soluble bioactive agents can in principle be enhanced by the following three technological manipulations:

BSPR:
For example, improvement of the bioavailability after peroral administration due to enhancement of the rate of dissolution by micronization has been described for digoxin (Shaw, T. R. D., Carless. J. E., Europ. J. Clin. Pharmacol., 7 (1974) 269) und griseofulvin (Atkinson, R. M., Bedford, C., Child, K. J., Tomich, E. G., Nature 193 (1962) 588). Micronization is the comminution of agglomerates to microcrystals of a size between 1 and 30 .mu.m by means of appropriate comminution equipment such as vibration mills, fluid-energy mills and colloid mills. Micronized substances can, however, exhibit wettability problems, e.g. due to aerophilization during the milling process. The reduced wettability counteracts to the increased dissolution rate achievable by micronization as a result of the reduced particle size and can therefore lead to a reduced dissolution rate.

BSPR:
A further reduction from the micrometer to the nanometer size range, e.g. in order to further enhance the bioavailability or to render possible parenteral, in particular intravenous administration, is practically not feasible with the conventional equipment used for micronization or requires a tremendous technological effort, and is therefore extremely costly and in many cases ineffective. Additionally, the reduction of solids to submicron-sized powders can bring about heavy difficulties in handling of these dry products such as an increased risk of dust explosions and cross-contamination problems in a factory environment. Moreover, such systems present a risk to health for persons exposed to the possible inhalation and absorption of potent bioactive materials.

BSPR:
For many applications there is, however, an obvious need to reduce the particle size down to the nanometer range. Thus particle size is an important factor with respect to the parenteral, in particular intravenous administration of drugs. As already mentioned before, many lipophilic drugs can not be formulated as aqueous solutions due to their low aqueous solubility. Intravenous administration of suspensions to sparingly soluble substances in water bears the risk of capillary blockage and embolism since the suspended particles are generally larger than the smallest blood vessels.

BSPR:
Drug carrier systems in the micrometer size range are represented by microspheres consisting of a solid polymer matrix, and microcapsules in which a liquid or a solid phase is surrounded and encapsulated by a polymer film. Nanoparticles consist, like microspheres, of a solid polymer matrix, however their mean particle size lies in the nanometer range. Both micro- and nanoparticles are generally prepared either by emulsion polymerization or by solvent evaporation techniques. Due to these production methods, micro- and nanoparticles bear the risk of residual contaminations from the production process like organic solvents such as chlorinated hydrocarbons, as well as toxic monomers, surfactants and cross-linking agents which can lead to toxicological problems. Moreover, some polymeric materials such as polylactic acid and polylactic-glycolic acid degrade very slowly in vivo so that multiple administration could lead to polymer accumulation associated with adverse side effects. Other polymers such as polyaikylcyanoacrylates release toxic formaldehyde on degradation in the body. Furthermore, microparticulate carriers are not suited for intravenous administration due to their size in the micrometer range.

BSPR:
A slow release composition of fat or wax and a biologically active protein, peptide or polypeptide suitable for parenteral administration to animals is disclosed in U.S. Pat. No. 895,608 lodged Aug. 11, 1986 to Staber, Fishbein and Cady (EP-A-0 257 368). The systems are prepared by spray drying and consist of spherical particles in the micrometer size range up to 1,000 microns so that intravenous administration is not possible. The latter also applies to wax microparticles described by Bodmeier et al. (Bodmeier R., Wang J., Bhagwatwar, J. Microencapsulation 9 (1992) 89-98), or to ibuprofen containing microspheres of cetostearic alcohol reported by Wong et al. (Won, L. P., Gilligan C. A., Li Wan

Po A., Int. J. Pharm. 83 (1992) 95-114). Both systems can be prepared by crude dispersion of the molten lipid using a high speed stirrer.

BSPR:
In an attempt to improve the intestinal absorption of lipophilic drugs, Eldem et al. (Eldem T., Speiser P., Hincal A., Pharm. Res. 8 (1991) 47-54) prepared lipid micropellets by spray-drying and spray-congealing processes. The micropellets are described as solid. spherical particles with smooth surfaces. The lipids are present in the crystalline state. Due to the particle size in the micrometer range these micropellets cannot be used for intravenous administration.

BSPR:
Beside applicability by the parenteral route, particle size is also an important parameter governing the activity of the reticuloendothelial system (RES). Upon intravenous administration colloidal particles are in general rapidly removed from the blood stream by cells of the RES such as phagocytic macrophages. The rate of blood clearance by the RES depends inter alia on the size of the colloidal particles. Larger particles are generally cleared more rapidly than smaller ones so that the latter have a longer circulation time in blood and thereby a higher probability of the incorporated drug to reach its target site.

BSPR:
Beside the particle size effect, the rate of RES uptake is inter alia governed by the surface characteristics of the colloidal particles such as surface charge and surface hydrophilicity. It is generally accepted that colloidal particles should he uncharged and hydrophilic in order to avoid RES uptake. Thus there is a possibility to divert colloidal particles away from the RES by modifying their surface characteristics, e.g. by coating with polymers (Troster S. D., Muller U., Kreuter J., Int. J. Pharm. 61 (1990) 85).

BSPR:
Surface properties play also an important role with regard to the dissolution process, e.g. in the GIT after peroral administration of poorly water soluble substances, and are therefore related to the bioavailability. Since apolar surfaces are only poorly wetted in aqueous media, another approach to increase the dissolution rate of sparingly water-soluble substances is thus hydrophilization of particle surfaces. From the field of pharmaceutical technology it is known that suitable surfactants are added to milled. hydrophobic powders as wetting agents in order to increase the wettability. Hydrophilization of apolar surfaces of poorly water-soluble bioactive agents can be obtained inter alia by processing these substances with water-soluble additives such as polyvinylpyrrolidone or polyethyleneglycol into spray-embeddings or co-precipitates.

BSPR:
Apart from reduction of particle size and improvement of wettability, the peroral bioavailability of a poorly water-soluble drug can be enhanced if the drug is not present in a crystalline but in an amorphous physical state. In general, amorphous forms of a substance exhibit a higher solubility and a faster dissolution than their crystal forms since the dissolution of amorphous substances does not require lattice energy. It is known, for example, that the antibiotic agent novobiocin can only be absorbed from the intestinum after administration of the amorphous substance which has a solubility ten times higher than the crystalline agent (Mullins J. D., Macek T. J., J. Am. Pharm. Assoc., Sci. Ed. 49 (1960) 245).

BSPR:
The bloavailability of ubidecarenone is generally low due to the poor solubility in gastrointestinal fluids causing a low gastrointestinal absorption of the substance. Kishi et al. (in Folkers K., Yamamura Y., (Eds.). Biomediacal and Clinical Aspects of Coenzyme Q, Vol. 4, Elsevier 1984, pp. 131-142) observed that the peroral bioavailability of ubidlecarenone from solid dosage forms such as tablets and granules is related to the dissolution rate of the preparations. Kanamori et al. (Yakuzaigaku 45 (1985) 119-126) also report that the bioavailability of perorally administered ubidecarenone depends on the dosage form and decreases in the order soft gelatin capsule, granules and tablets.

BSPR:
A number of different formulations with the object to enhance the bioavailability of ubidecarenone can be found in the patent literature. Taki and Takahira

disclose in EP 23349 (04.02.81) that the lymphatic absorption of orally administered ubidecarenone is increased by coadministration of long-chain fatty acids and monoglycerides. Increase of intestinal absorption by administration of capsules containing oily (surfactant) solutions of ubidecarenone is disclosed in different patents such as WO 8604503 A1 (14.08.86), JP 63188623 A2 (04.08.88), JP 62067019 A2 (26.03.87), JP 59148735 A2 (25.08.84) and JP 56012309 (06.02.81). Solubilization of ubidecarenone in micellar solutions is described in EP 522433 A1 (13.01.93), WO 8803019 A1 (05.05.88) and JP 59148718 A2 (25.08.84). Ueno et al. (Acta Pharm. Nord., 1 (1989) 99-104) report on the increase of peroral bioavailability by inclusion of ubidecarenone in a complex with .beta.-cyclodextrins. A similar formulation is disclosed in JP 56109590 A2 (31.08.81). Moreover, incorporation of ubidlecarenone in emulsions is reported to enhance intestinal absorption as described, for example, by Yano et al. in EP 494654 A2 (15.07.92).

BSPR:
From what is outlined above it is evident that ubidecarenone is a problematic substance with regard to pharmaceutical formulations of this drug. There are, however, by far more sparingly water soluble substances with similar formulation problems. The peroral bioavailability of these substances is poor due to the low aqueous solubility, and the intravenous administration is also problematic due to the lack of suitable intravenous formulations.

BSPR:
The present invention introduces a novel and improved administration system for sparingly water-soluble and poorly wettable bioactive substances, in particular for ubidecarenone, based on dispersions or redispersible preparations of micron and, preferably, submicron-sized (colloidal) particles of poorly water-soluble substances which are solid, in particular crystalline, at room temperature in the bulk phase characterized in that the dispersed substance is primarily present in an amorphous physical state, in particular a liquid one, e.g. a supercooled melt. This administration system which is referred to as particles of supercooled melt (PSMs) has several advantages over conventional formulations which arise inter alia from the modified physical state of the substance in the (colloidal) particles, and provides for an improved bioavailability as well as for the direct parenteral, in particular intravenous administration of poorly water-soluble bioactive substances. PSMs can also be employed as a carrier system for poorly water-soluble bioactive agents, in particular for parenteral administration. Moreover, the invention also relates to a method to prepare this novel administration system characterized in that the process avoids the use of toxicological additives such as organic sovents, e.g. chlorinated hydrocarbons, and yields a product which is easy to handle from the security point of view since it is present as a dispersion in a pharmaceutically acceptable liqiud, preferably aqueous media.

BSPR:
The present invention relates to (colloidal) PSMs and their dispersions in pharmaceutically acceptable liquids, to a method for the manufacture thereof as well as to their use as an administration system for poorly water-soluble bioactive agents.

BSPR:
The PSMs of the present invention typically have particle size distributions in the low micrometer and in the nanometer size range with mean particle diameters determined by photon correlation spectroscopy (PCS) ranging predominantly from 30 to 500 nm. The particle core of PSMs consists of one or more poorly water-soluble substances which are primarily present in an amorphous, non-crystalline state, preferably as a supercooled melt.

BSPR:
PSMs of ubidecarenone manufactured according to the procedure described above represent predominantly spherical particles of submicron size and which are predominantly present in an amorphous state at room temperature, more specifically as a supercooled melt, i.e. as a liquid. Ubidecarenone-PSMs consist of an amorphous, predominantly liquid core of ubidecarenone which is covered by one or more layers of preferably physiological or toxicologically inert stabilizers. By a proper choice of stabilizing agents the particle surface properties can be modified. Ubidecarenone-PSMs can be distinguished from conventional formulations of ubidecarenone by their modified physicochemical properties such as their structure (liquid physical state of a supercooled melt),

their physicochemical properties (e.g. modified surface characteristics) and their particle size (nanometer size range). Ubidecarenone-PSMs can be applied for the enteral, parenteral and topical administration of ubidecarenone as well as of other substances which can be incorporated into ubidecarenone-2 PSMs. The release of incorporated drugs can be controlled to a certain extent by the choice of stabilizing agents surrounding the particle core. Compared to drug carrier vehicles based on lipid emulsions, ubidecarenone-PSMs have the advantage that they are less rapidly degraded in the blood than triglycerides of lipid emulsions. Thus drug release can be sustained. Since ubidecarenone is nontoxic, ubidecarenone-PSMs can be applied in high doses. Moreover, disadvantages of carrier systems (e.g. lipid emulsions, lipid suspensions, dispersions of liquid crystalline phases) such as low drug pay load of the carrier or side effects caused by the carrier particles themselves can be circumvented by the use of PSMs.

BSPR:
It can be theoretically deduced that PSMs analogous to those of ubidecarenone can principally be prepared from other substances as well, and this has been confirmed experimentally as described in the Examples listed below. Substances which are particularly suited for the preparation of aqueous PSM dispersions are characterized by a poor solubility in aqueous media. They have a melting point preferably below approximately 100-130.degree. C. or their melting point can be decreased to below 100-130.degree. C. by the addition of additives which decrease the melting point, and/or their recrystallization from the melt is impaired or inhibited or can be impaired or inhibited by the addition of additives. Substances with these properties can be bioactive agents which exhibit a poor bioavailability after peroral administration due to their low solubility in Gastrointestinal fluids, or the formulation of which as a parenteral dosage form is problematic; or pharmacologically acceptable substances which are suited as carrier materials for poorly water-soluble drugs or other bioactive agents; or bioactive agents the industrial processing and handling of which shall be improved. Suitable substances with these properties can be found in the Examples listed below. The physicochemical properties of the substance which determine the properties of the fine dispersed material, that means if the dispersed substance exists in an amorphous, preferably liquid, i.e. supercooled state over a longer period of time, or transforms into a solid crystalline state, are given by the Thomson equation via the ratio of the melting point T of small particles of radius r and the normal melting point T.sub.O of the bulk material

BSPR:
Substances particularly suitable for the entrapment into PSMs are drugs or other bioactive compounds which are poorly water-soluble, show a low bioavailability, are badly absorbed from the intestinum, as well as low-specific active substances which are highly toxic at non-target sites. In case it is desired to incorporate a relatively water soluble compound into PSMs, it might be necessary to decrease the solubility of this compound in the dispersion medium which can be achieved, for example, by using a water insoluble derivative of the compound such as an acid or base, a complex, or a lipophilic precursor.

BSPR:
The advantages of aqueous PSM dispersions over conventional formulations for the administration of poorly water-soluble drugs can bc deduced from the characteristics of PSMs as described above, in particular from the combination of the amorphous state of the particles at body and room temperature, their small particle size and their hydrophilized surfaces. The present invention is therefore supposed to bring about the following advantages:

BSPL:
and comprise the surface tension of the solid .gamma.SL, the molar volume of the solid V.sub.S, the particle/grain size, and the heat of fusion .DELTA.H.sub.fus (Hunter R. J. (1986) "Foundations of Colloid Science", Vol. 1, Oxford University Press, Oxford, p. 268). They are thus inter alia related to the complexity of the crystal lattice of the bulk material. With respect to the size dependence of the physical state of the dispersed particles, a smaller particle size generally favours the liquid state of a supercooled melt. The critical size below which a substance is predominantly present in an amorphous liquid state is, however, different for different substances and depends also on other physicochemical properties of the substances, e.g. such as listed above, in particular on the crystallization tendency of the substance. Furthermore the physical state of dispersed particles can be influenced by the presence of surface active

stabilizing agents, and might also be influenced by the temperature treatment after dispersion of the molten substance. It is therefore possible that particles with different properties concerning their physical state might be obtained by basically the same manufacturing process depending on the physicochemical properties of the bulk material which is dispersed, as well as on the process parameters such as e.g. homogenization time and homogenization pressure since the latter influence the size of the dispersed particles. Thus particles with a solid interior phase, e.g. lipid suspensions described by Domb and Maniar in U.S. Pat. No. 435,546 or by Westesen et al. (Westesen K., Siekmann B., Koch M. H. J., Int. J. Pharm. 93 (1993) 189-199). can also be prepared by a melt emulsification process. The product of the process is, however, different from PSMs with respect to the physical state of the dispersed phase. In the dispersion process disclosed by Domb and Maniar in U.S. Pat. No. 435,546 the molten and dispersed particles are forced into the solid state by a temperature treatment, e.g. fast cooling after emulsification. During the production of solid lipid nanoparicles by melt emulsification according to Westesen et al. (Westesen K., Siekmann B., Koch M. H. J., Int. J. Pharm. 93 (1993) 189-199), the metastable state of a supercooled melt of the lipids might be passed temporarily, but due to the physicochemical properties of the lipids employed for the preparation of solid lipid nanoparticles, such as e.g. the high crystallization tendency, these lipids recrystallize within a relatively short period alter production to form solid particles.

BSPV:
reduction of particle size,

BSPV:
5. The (predispersed) melt is emulsified in the dispersion medium, preferably at temperatures above the melting point of the substance or the mixture of substances or the mixture of substances and additives, e.g,. stabilizers, respectively. Emulsification is preferably carried out by high pressure homogenization or by sonication, but may be also possible by high speed stirring, vortexing and vigorous hand shaking. The way of homogenization determines the particle size distribution and the mean particle size of PSMs.

BSPV:
1. Since the bioactive substance formulated as PSMs is completely or partly present in an amorphous physical state, preferably in the liquid state, e.g. a supercooled melt, dissolution of the substance does not require or, respectively, requires less energy than the crystalline substance which needs to overcome lattice forces. The dissolution rate of PSMs is therefore increased as well as its solubility resulting in an enhanced bioavailability compared to the crystalline bulk substance.

BSPV:
3. The .small particle size of PSMs in the nanometer size range can generally not be achieved by conventional comminution techniques such as milling, grinding or micronization. The small particle size results in a tremendous increase of the specific surface area compared to conventional administration systems such as (micronized) powders or granulates. Since the solubility is related to particle size via the dissolution rate, size reduction results in an increased dissolution rate. It is well known that the peroral bioavailability of bioactive agents depends on their dissolution rate in gastrointestinal fluids. Consequently, the bioavailability of bioactive agents formulated as colloidal PSMs can be improved.

BSPV:
4. Formulation of PSMs according to the present invention with particle sizes in the nanometer size range renders possible the direct parenteral administration of practically water-insoluble substances. Due to the small particle size of PSMs, dispersions thereof can be administered intravenously without risk of embolism which is not possible for the crystalline bulk substance suspended in an aqueous medium.

BSPV:
5. The achievable particle size of PSMs is below 150 nm which corresponds to the diameter of the fenestrations of the endothelial wall of blood vessels. Intravenously administered PSMs therefore have the potential to leave the vascular compartment via these fenestrations. Drugs formulated as PSMs or incorporated into PSMs can thus be transported within the particles to

extravascular targets such as the bone marrow or tumor tissues.

BSPV:
6. Since PSMs are covered by stabilizing agents, they have hydrophilic surfaces and therefore exhibit a good wettability. A good wettability, e.g. in the gastro-intestinal tract, facilitates the dissolution of the substance which leads to an improved bioavailability.

DEPR:
The mean particle size (number distribution) of the dispersion is determined by photon correlation spectroscopy (PCS: Zetasizer 3, Malvern) to be 102.5 nm.

DEPR:
The mean particle size (number distribution) of the dispersion determined by PCS is 68.5 nm. Ubidecarenone nanoparticles display a narrow particle size distribution (FIG. 1). For comparison, FIG. 2 illustrates the particle size distribution of the powdered raw material of ubidecarenone used for preparation of the nanoparticles as determined by laser diffractometry (Mastersizer, Malvern). For the measurement the powder was dispersed in an aqueous solution of 0.3% sodium glycocholate. The particle size distribution of the powders ranges from the lower micrometer up to the millimeter size range. The complete distribution can, however, not be completely determined due to the limited measurement range of the instrument (up to 600 .mu.m). The volume distribution mean with respect to the covered measurement range is 237.5 .mu.m.

DEPR:
In order to estimate the stability on storage of the aqueous dispersions of ubidecarenone prepared according to Example 1 and 2, the particle size of the dispersions stored at 4.degree. C. was repeatedly determined by PCS at different time intervals over a monitored period of 30 months. FIG. 3 presents the mean particle size of ubidecarenone nanoparticles of Example 1 and 2 versus storage time. The mean particle is practically constant over the monitored period of 30 months. Ubidecarenone nanoparticles thus exhibit an excellent stability on storage.

DEPR:
The mean particle size (number distribution) determined by PCS is 69.9 nm. FIG. 4 illustrates the time course of particle comminution by microfluidizer homogenization. During homogenization small sample volumes for size analysis were taken from the dispersion after each minute. The particle size of ubidecarenone particles is decreasing with homogenization time. The graph levels off asymptotically, i.e. when a certain size limit is reached the particle size cannot be further reduced by additional homogenization cycles.

DEPR:
4.0 g ubidecarenone is melted in a thermostatized vessel at 70.degree. C. 2.4 g lecithin (Phospholipon 100, Nattermann) is dispersed in the melt by sonication (Soniprep, MSE). 500 mg sodium glycocholate is dissolved in 33.1 g bidistilled water, and the solution is heated to 70.degree. C. The heated aqueous phase is added to the dispersion of lecithin in molten ubidecarenone. The warm mixture is predispersed by sonication (Soniprep, MSE) for 3 min. The predispersion is homogenized at 500 bar for 5 cycles in a high pressure homogenizer type Micron Lab 40 (APV Gaulin) which was heated to 80.degree. C. The dispersion is allowed to stand at room temperature for cooling.

DEPR:
The mean particle size (number distribution) determined by PCS is 144 nm.

DEPR:
1.2 g ubidecarenone is melted in a thermostatized vessel at 70.degree. C. 840 mg tyloxapol is dissolved in 38.0 g bidistilled water heated to 70.degree. C. The heated aqueous phase is added to the melt of ubidecarenone. The warm mixture is predispersed by sonication (Soniprep, MSE) for 3 min. The predispersion is homogenized at 1200 bar for 10 cycles in a high pressure homogenizer type Micron Lab 40 (APV Gaulin) which was heated to 80.degree. C. The dispersion is allowed to stand at room temperature for cooling.

DEPR:
The mean particle size (number distribution) determined by PCS is 67.3 nm.

DEPR:
A wide angle X-ray diffraction pattern of the aqueous ubidecarenone dispersion prepared according to Example 1 is recorded. The aqueous dispersion is filled into a sample cell thermostatized at 20.degree. C. Due to the small particle size and the relatively low concentration of ubidecarenone in the dispersion it can be assumed that crystalline portions of the substance, which could be possibly present in the dispersions, cannot be detected by a conventional X-ray source. X-ray measurements were therefore performed by use of a synchrotron radiation source at the storage ring DORIS of the Deutsches Elektronen Synchrotron (DESY), Hamburg. Reflections were recorded in the observation range 1.7

DEPR:
1.2 g ubidecarenone is melted in a thermostatized vessel at 70.degree. C. 150 mg lecithin (Phospholipon 100, Nattermann) is dispersed in the melt by sonication (Soniprep, MSE). 50 mg sodium glycocholate is dissolved in 38.7 g deuterium oxide (deuterated water), and the solution is heated to 70.degree. C. The heated aqueous phase is added to the dispersion of lecithin in molten ubidecarenone. Probe sonication (Soniprep, MSE) for 60 min at 70.degree. C. yields a fine dispersion of ubidecarenone nanoparticles. The dispersion is allowed to stand at room temperature for cooling. The mean particle size (number distribution) determined by PCS is 141.3 nm.

DEPR:
160 mg sodium glycocholate is dissolved in 37.9 g bidistilled water. 720 mg lecithin (Lipoid S 100, Lipoid KG) is dispersed in the solution by magnetic stirring for several hours. 1.2 g ubidecarenone is melted in a thermrostatized vessel at 70.degree. C. The aqueous phase is heated to 70.degree. C., and is added to the melt of ubidecarenone. A predispersion is prepared by sonication which is homogenized for 10 cycles at 1200 bar in a high pressure homogenizer type Micron Lab 40 thermostatized at 80.degree. C. The dispersion is allowed to stand at room temperature for cooling.

DEPR:
1.2 g ubidecarenone is melted in a thermostatized vessel at 70.degree. C. 720 mg lecithin (Lipoid S 100, Lipoid KG) is dispersed in the melt by sonication (Soniprep, MSE). 40 mg retijiol (vitamin A) is dissolved in the melt 160 mg sodium glycocholate is dissolved in 37.9 g bidistilled water, and the solution is heated to 70.degree. C. The heated aqueous phase is added to the retinol containing dispersion of lecithin in molten ubidecarenone. The warm mixture is predispersed by sonication (Soniprep, MSE) for 3 min. The predispersion is homogenized at 1200 bar for 10 cycles in a high pressure homogenizer type Micron Lab 40 (APV Gaulin) thermostatized at 80.degree. C. The dispersion is allowed to stand at room temperature for cooling.

DEPR:
The mean particle size (number distribution) determined by PCS is 110.9 nm. Repeated DSC measurements according to the description in Example 8 at different time intervalls during storage of the sample in a refrigerator do not reveal any thermal transition.

DEPR:
1.2 g ubidecarenone is melted in a thermostatized vessel at 70.degree. C. 720 mg lecithin (Lipoid S 100, Lipoid KG) is dispersed in the melt by sonication (Soniprep, MSE). 40 mg menadione (vitamin K.sub.3) is dissolved in the melt. 160 mg sodium glycocholate is dissolved in 37.9 g bidistilled water, and the solution is heated to 70.degree. C. The heated aqueous phase is added to the retinol containing dispersion of lecithin in molten ubidecarenone. The warm mixture is predispersed by sonication (Soniprep, MSE) for 3 min. The predispersion is homogenized at 1200 bar for 10 cycles in a high pressure homogenizer type Micron Lab 40 (APV Gaulin) thermostatized at 80.degree. C. The dispersion is allowed to stand at room temperature for cooling.

DEPR:
The mean particle size (number distribution) determined by PCS is 102.0 nm. Repeated DSC measurements according to the description in Example 8 at different time intervalls during storage of the sample in a refrigerator do not reveal any thermal transition.

DEPR:
1.0 colecalciferol is melted. 1.25 g glycerol (70%) and 4 mg thiomersal are dissolved in 37.5 g bidistilled water. 240 mg soya lecithin (Lipoid S 100, Lipoid

KG) is dispersed in the aqueous solution by probe sonication (MSE Soniprep). 80 mg sodium glycocholate is dissolved in this dispersion. The aqueous phase is heated to 95.degree. C. and is added to the melt of colecalciferol. The mixture is predispersed by probe sonication in a thermostatized vessel at 95.degree. C. The predispersion is passed five times through a high pressure homogenizer (APV Gaulin Micron Lab 40) thermostatized at 95.degree. C. The homogenization pressure is 800 bar. The dispersion of PSMs is allowed to stand at room temperature for cooling.

DEPR:
The mean particle size (number distribution) determined by PCS is 216.1 nm after preparation. The DSC thermogram of the PSM dispersion of colecalciferol does not reveal any transition peak in the temperature range from 20 to 95.degree. C. pointing to the presence of amorphous particles of colecalciferol.

DEPR:
800 mg colecalciferol is melted. 120 mg soya lecithin (Lipoid S 100, Lipoid KG) is dispersed in the melt by probe sonication (MSE Soniprep). 1.2 g glycerol (70%), 40 mg sodium glycocholate and 4 mg thiomersal are dissolved in 36.5 g bidistilled water. The aqueous phase is heated to 95.degree. C. and is added to the melt. The mixture is predispersed by probe sonication in a thermostatized vessel at 95.degree. C. The predispersion is passed five times through a high pressure homogenizer (APV Gaulin Micron Lab 40) thermostatized at 95.degree. C. The homogenization pressure is 800 bar. The dispersion of PSMs is allowed to stand at room temperature for cooling. The mean particle size (number distribution) determined by PCS is 321 nm.

DEPR:
2.0 g tocopherol acid succinate is melted. 1.2 glycerol (70%) and 4 mg thiomersal are dissolved in 36.5 g bidistilled water. 490 mg soya lecithin (Lipoid S 100, Lipoid KG) is dispersed in the aqueous solution by probe sonication (MSE Soniprep). 160 mg sodium glycholate is dissolved in this dispersion. The aqueous phase is heated to 90.degree. C. and is added to the melt of tocopherol acid succinate. The mixture is predispersed by probe sonication in a thermostatized vessel at 90.degree. C. The predispersion is passed five times through a high pressure homogenizer (APV Gaulin Micron Lab 40) thermostatized at 90.degree. C. The homogenization pressure is 800 bar. The dispersion of PSMs is allowed to stand at room temperature for cooling.

DEPR:
The mean particle size by number after preparation is 188.7 nm determined by PCS.

DEPR:
4.0 g cholesteryloleate is melted. 970 mg soya lecithin (Lipoid S 100, Lipoid KG) is dispersed in the melt by probe sonicalion (MSE Soniprep). 1.1 glycerol (70%), 240 mg sodium glycocholate and 4 mg thiomersal are dissolved in 34.8 g bidistilled water. The aqueous phase is heated to 60.degree. C. and is added to the melt. The mixture is predispersed by probe sonication in a thermostatized vessel at 60.degree. C. The predispersion is passed five times through a high pressure homogenizer (APV Gaulin Micron Lab 40) thermostatized at 80.degree. C. The homogenization pressure is 800 bar. The dispersion of PSMs is allowed to stand at room temperature for cooling. The mean particle size by number after preparation is 176.4 nm determined by PCS.

DEPR:
4.0 g cholesteryloleate is melted and 200 mg of the heart protecting drug ubidecarenone is dissolved in the melt. 970 mg soya lecithin (Lipoid S 100, Lipoid KG) is dispersed in the melt by probe sonication (MSE Soniprep). 1.1 g glycerol (70%), 240 mg sodium glycocholate and 4 mg thiomersal are dissolved in 34.8 g bidistilled water. The aqueous phase is heated to 60.degree. C. and is added to the melt. The mixture is predispersed by probe sonication in a thermostatized vessel at 60.degree. C. The predispersion is passed five times through a high pressure homogenizer (APV Gaulin Micron Lab 40) thermostatized at 80.degree. C. The homogenization pressure is 800 bar. The drug-loaded dispersion of PSMs is allowed to stand at room temperature for cooling. The particle size distribution is similar to that of Example 17.

DEPR:
4.0 g trimyristate (Dynasan 114, Huls AG, Witten) is melted. 640 mg soya lecithin

KG) is dispersed in the aqueous solution by probe sonication (MSE Soniprep). 80 mg sodium glycocholate is dissolved in this dispersion. The aqueous phase is heated to 95.degree. C. and is added to the melt of colecalciferol. The mixture is predispersed by probe sonication in a thermostatized vessel at 95.degree. C. The predispersion is passed five times through a high pressure homogenizer (APV Gaulin Micron Lab 40) thermostatized at 95.degree. C. The homogenization pressure is 800 bar. The dispersion of PSMs is allowed to stand at room temperature for cooling.

DEPR:
The mean particle size (number distribution) determined by PCS is 216.1 nm after preparation. The DSC thermogram of the PSM dispersion of colecalciferol does not reveal any transition peak in the temperature range from 20 to 95.degree. C. pointing to the presence of amorphous particles of colecalciferol.

DEPR:
800 mg colecalciferol is melted. 120 mg soya lecithin (Lipoid S 100, Lipoid KG) is dispersed in the melt by probe sonication (MSE Soniprep). 1.2 g glycerol (70%), 40 mg sodium glycocholate and 4 mg thiomersal are dissolved in 36.5 g bidistilled water. The aqueous phase is heated to 95.degree. C. and is added to the melt. The mixture is predispersed by probe sonication in a thermostatized vessel at 95.degree. C. The predispersion is passed five times through a high pressure homogenizer (APV Gaulin Micron Lab 40) thermostatized at 95.degree. C. The homogenization pressure is 800 bar. The dispersion of PSMs is allowed to stand at room temperature for cooling. The mean particle size (number distribution) determined by PCS is 321 nm.

DEPR:
2.0 g toccpherol acid succinate is melted. 1.2 glycerol (70%) and 4 mg thiomersal are dissolved in 36.5 g bidistilled water. 490 mg soya lecithin (Lipoid S 100, Lipoid KG) is dispersed in the aqueous solution by probe sonication (MSE Soniprep). 160 mg sodium glycholate is dissolved in this dispersion. The aqueous phase is heated to 90.degree. C. and is added to the melt of tocopherol acid succinate. The mixture is predispersed by probe sonication in a thermostatized vessel at 90.degree. C. The predispersion is passed five times through a high pressure homogenizer (APV Gaulin Micron Lab 40) thermostatized at 90.degree. C. The homogenization pressure is 800 bar. The dispersion of PSMs is allowed to stand at room temperature for cooling.

DEPR:
The mean particle size by number after preparation is 188.7 nm determined by PCS.

DEPR:
4.0 g cholesteryloleate is melted. 970 mg soya lecithin (Lipoid S 100, Lipoid KG) is dispersed in the melt by probe sonicalion (MSE Soniprep). 1.1 glycerol (70%), 240 mg sodium glycocholate and 4 mg thiomersal are dissolved in 34.8 g bidistilled water. The aqueous phase is heated to 60.degree. C. and is added to the melt. The mixture is predispersed by probe sonication in a thermostatized vessel at 60.degree. C. The predispersion is passed five times through a high pressure homogenizer (APV Gaulin Micron Lab 40) thermostatized at 80.degree. C. The homogenization pressure is 800 bar. The dispersion of PSMs is allowed to stand at room temperature for cooling. The mean particle size by number after preparation is 176.4 nm determined by PCS.

DEPR:
4.0 g cholesteryloleate is melted and 200 mg of the heart protecting drug ubidecarenone is dissolved in the melt. 970 mg soya lecithin (Lipoid S 100, Lipoid KG) is dispersed in the melt by probe sonication (MSE Soniprep). 1.1 g glycerol (70%), 240 mg sodium glycocholate and 4 mg thiomersal are dissolved in 34.8 g bidistilled water. The aqueous phase is heated to 60.degree. C. and is added to the melt. The mixture is predispersed by probe sonication in a thermostatized vessel at 60.degree. C. The predispersion is passed five times through a high pressure homogenizer (APV Gaulin Micron Lab 40) thermostatized at 80.degree. C. The homogenization pressure is 800 bar. The drug-loaded dispersion of PSMs is allowed to stand at room temperature for cooling. The particle size distribution is similar to that of Example 17.

DEPR:
4.0 g trimyristate (Dynasan 114, Huls AG, Witten) is melted. 640 mg soya lecithin

(Lipoid S 100, Lipoid KG) is dispersed in the melt by probe sonication (MSE Soniprep). 1.0 g glycerol, 160 mg sodium glycocholate and 4 mg thiomersal are dissolved in 34.2 g bidistilled water. The aqueous phase is heated to 70.degree. C. and is added to the melt. The mixture is predispersed by probe sonication in a thermostatized vessel at 70.degree. C. The predispersion is passed five times through a high pressure homogenizer (APV Gaulin Micron Lab 40) thermostatized at 80.degree. C. The homogenization pressure is 800 bar. The dispersion of PSMs is allowed to stand at room temperature for cooling. The mean particle size by number after preparation is 109.4 nm determined by PCS.

DEPR:
4.0 g Witepsol H42 (Huls AG, Witten) is melted. 800 mg soya lecithin (Lipoid S 100, Lipoid KG) is dispersed in the melt by probe sonication (MSE Soniprep). 1.0 g glycerol, 800 mg tyloxapol and 4 mg thiomersal are dissolved in 33.4 g bidistilled water. The aqueous phase is heated to 60.degree. C. and is added to the melt. The mixture is predispersed by probe sonication in a thermostatized vessel at 60.degree. C. The predispersion is passed five times through a high pressure homogenizer (APV Gaulin Micron Lab 40)) thermostatized at 80.degree. C. The homogenization pressure is 800 bar. The dispersion of PSMs is allowed to stand at room temperature for cooling. The mean particle size by number after preparation is 62.6 nm determined by PCS.

DEPR:
4.0 g Witepsol H35 (Huls AG, Witten) is melted. 640 mg soya lecithin (Lipoid S 100, Lipoid KG) is dispersed in the melt by probe sonication (MSE Soniprep). 1.0 g glycerol, 160 mg sodium glycocholate and 4 mg thiomersal are dissolved in 34.2 g bidistilled water. The aqueous phase is heated to 60.degree. C. and is added to the melt. The mixture is predispersed by probe sonication in a thermostatized vessel at 60.degree. C. The predispersion is passed five times through a high pressure homogenizer (APV Gaulin Micron Lab 40) thermostatized at 80.degree. C. The homogenization pressure is 800 bar. The dispersion of PSMs is allowed to stand at room temperature for cooling. The mean particle size by number after preparation is 106.9 nm determined by PCS.

DEPR:
4.0 g Witepsol H42 (Huls AG, Witten) is melted. 800 mg soya lecithin (Lipoid S 100 Lipoid KG) is dispersed in the melt by probe sonication (MSE Soniprep). 40 mg taxol is dissolved in the melt. 1.0 g glycerol, 800 mg tyloxapol and 4 mg thiomersal are dissolved in 33.4 g bidistilled water. The aqueous phase is heated to 60.degree. C. and is added to the melt. The mixture is predispersed by probe sonication in a thermostatized vessel at 60.degree. C. The predispersion is passed five times through a high pressure homogenizer (APV Gaulin Micron Lab 40) thermostatized at 80.degree. C. The homogenization pressure is 800 bar. The dispersion of PSMs is allowed to stand at room temperature for cooling.

DEPR:
4.0 g Witepsol H42 (Huls AG, Witten) is melted. 800 mg soya lecithin (Lipcid S 100, Lipoid KG) is dispersed in the melt by probe sonication (MSE Soniprep). 20 mg estramustin is dissolved in the melt. 1.0 glycerol, 800 mg tyloxapol and 4 mg thiomersal are dissolved in 33.4 g bidistilled water. The aqueous phase is heated to 60.degree. C. and is added to the melt. The mixture is predispersed by probe sonication in a thermostatized vessel at 60.degree. C. The predispersion is passed five times through a high pressure homogenizer (APV Gaulin Micron Lab 40) thermostatized at 80.degree. C. The homogenization pressure is 800 bar. The dispersion of PSMs is allowed to stand at room temperature for cooling.

DEPR:
4.0 g Witepsol H42 (Huls AG, Witten) is melted. 800 mg soya lecithin (Lipoid S 100, Lipoid KG) is dispersed in the melt by probe sonication (MSE Soniprep). 200 mg ubidecarenone is dissolved in the melt. 1.0 g glycerol, 800 mg tyloxapol and 4 mg thiomersal are dissolved in 33.4 g bidistilled water. The aqueous phase is heated to 60.degree. C. and is added to the melt. The mixture is predispersed by probe sonication in a thermostatized vessel at 60.degree. C. The predispersion is passed five times through a high pressure homogenizer (APV Gaulin Micron Lab 40) thermostatized at 80.degree. C. The homogenization pressure is 800 bar. The dispersion of PSMs is allowed to stand at room temperature for cooling.

DEPR:
4.0 g ubidecarenone is melted in a thermostatized vessel at 80.degree. C. 200 mg estramustin is dissolved in the melt. 500 mg sodium glycocholate and 1.0 g

glycercl are dissolved in 32.1 g bidistilled water. 2.4 g lecithin is dispersed in the solution by sonication (Soniprep, MSE). The aqueous phase is heated to 80.degree. C. and is added to the melt. The warm mixture is predispersed by sonication (Soniprep, MSE) for 3 min. The predispersion is homogenized at 800 bar for 5 cycles in a high pressure homogenizer type Micron Lab 40 (APV Gaulin) which is heated to 80.degree. C. The dispersion is allowed to stand at room temperature for cooling.

DEPR:
40 g ubidecarenone is melted in a thermostatized vessel at 80.degree. C. 200 mg estramustin is dissolved in the melt. 500 mg sodium glycocholate and 1.0 g glycerol are dissolved in 32.1 g bidistilled water. 2.4 g lecithin is dispersed in the solution by sonication (Soniprep, MSE). The aqueous phase is heated to 80.degree. C. and is added to the melt. The warm mixture is predispersed by sonication (Soniprep, MSE) for 3 min. The predispersion is homogenized at 800 bar for 5 cycles in a high pressure homogenizer type Micron Lab 40 (APV Gaulin) which is heated to 80.degree. C. The dispersion is allowed to stand at room temperature for cooling.

DEPR:
FIG. 1 Particle size distribution by number of ubidecarenone PSMs of Example 2 determined by photon correlation spectroscopy.

DEPR:
FIG. 2 Particle size distribution of crystalline ubidecarenone powder determined by laser diffractometry. For the measurement the powder was dispersed in an aqueous solution of 0.3% sodium glycocholate.

DEPR:
FIG. 3 Stability on storage of ubidecarenone PSMs of Examples 1 and 2: Dependence of the mean particle size (PCS number distribution) on storage time.

DEPR:
FIG. 4 Time course of homogenization in the Microfluidizer (Microfluidics Corp.): Dependence of the mean particle size of the ubidecarenone PSMs of Example 4 on homogenization time.

DEPR:
FIG. 6 Particle size distribution of the ubidecarenone PSMs of Example 5 determined by laser diffractometry.

CLPR:
1. Particles having a mean particle size of between 30 and 500 nm comprising

$1\,\mu = 10^{-6}\,m = 1000\,nm$

+n